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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,120	BACUS, SARAH S.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-13,16 and 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-13, 16, and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 6/16/04 is acknowledged and has been entered. Claim 21 has been amended. Currently, claims 2-13, 16, and 19-23 are pending and are under examination.

Rejections Withdrawn

2. In light of Applicant's amendment and argument, the rejection of claims 2-13, 16, and 19-23 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 2-11, 13, 16, and 19-23 stand rejected under 35 U.S.C. 103(a) as unpatentable over Slamon et al. (US Patent 5,846,749) in view of Veltri et al. (US Patent 6,463,438) for reason of record.

4. Claim 12 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Slamon et al. (US Patent 5,846,749) in view of Veltri et al. (US Patent

6,463,438) as applied to claims 2-11, 13, 16, and 20-23 above, and in further view of McNamara et al. (US Patent 6,007,996) for reason of record.

Response to Arguments

5. Applicant's arguments filed 6/16/04 have been fully considered but they are not persuasive.

A) Applicant argues that the cited references, alone or in combination, does not teach or suggest the claimed method wherein the average optical density of stained target protein per pixel of cellular area is determined by image analysis; hence, the actual cells do not need to be identified and the number of cells present in the image field does not need to be determined. Applicant contends that Slamon does not teach a method of determining an "average optical density of stained target protein per pixel of cellular area"; but instead quantitates surface membrane and cytosolic proteins by determining the optical signal value from a known number of cells and relates this value to values with the control cells, i.e. optical value per cell. Specifically, Applicant argues that the Slamon reference does not teach how to quantitate cellular proteins using image analysis without knowing or determining the number of cells immunostained.

In response, claim 21 recites "the method comprising the steps of" which is an open language; hence, the claimed invention does not exclude that the actual cells do not need to be determined and the number of cells do not need to be determined, and specifically does not exclude determining optical value from a known number of cells, as taught in the method of Slamon.

In as far as Slamon et al. failing to teach a method of determining an "average optical density of stained target protein per pixel of cellular area", which amounts to arguing against the reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This rejection is based on the combination of Slamon with Veltri. In this case, Slamon discloses a method of determining expression level of target protein in cells from a homogeneous cell population by immunohistochemically staining the cells in order to provide optical signal capable of quantitation by image analysis. Slamon uses two or more stained control cell pellets to relate the average optical signal from each pellet to the quantitative amount of target protein on the cells. Slamon discloses staining the cells using detectably-labeled antibodies directed against the target protein. The sample and control cell pellets are assayed at the same time so as to obtain a direct correlation between the amount of protein present in the cells per cell and the average optical density signal observed with the immunohistochemical staining. A calibration curve is prepared relating average optical signal observed with each pellet and the amount of target protein present in the pellet cells. The signal obtained from the sample is related to the concentration curve relating signal to concentration, to concentration of the target protein with known amounts of the protein in the control cell pellets. Veltri is combined with Slamon only for the teaching of determining optical density of stained target protein per pixel of

cell area, i.e. nuclear or cytoplasmic receptor cites, in a population of nucleated cells after immunostaining the target biomarker protein in the cells using biomarker specific antibody. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Veltri in determining optical density of stained target protein per pixel of cell area, into the method of Slamon because Veltri specifically taught that resulting values of such pixel measurement relate specifically to the target proteins specific in selected cell areas; thus, excludes measurement of nonspecific extraneous proteins.

B) Applicant argues that Veltri does not teach or suggest a method of determining an "average optical density of stained target protein per pixel of cellular area", followed by either "generating a calibration curve relating the known quantity of target protein with the average optical density of stained target protein per pixel of cellular area" or using such a calibration curve to determine the quantity of target protein in a biological sample. Applicant specifically contends that Veltri does not teach determining average optical density of stained target protein per pixel of cellular area without knowing or determining the individual cells that are being analyzed.

In response, claim 21 recites "the method comprising the steps of" which is an open language; hence, the claimed invention does not exclude that the individual cells being analyzed are not known or determined, as taught in the method of Veltri.

In as far as Veltri et al. failing to teach a method of determining an "average optical density of stained target protein per pixel of cellular area", followed by either "generating a calibration curve relating the known quantity of target protein with the average optical density of stained target protein per pixel of cellular area" or using such a calibration curve to determine the quantity of target protein in a biological sample, which amounts to arguing against the reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

This rejection is based on the combination of Slamon with Veltri. In this case, Slamon discloses a method of determining expression level of target protein in cells from a homogeneous cell population by immunohistochemically staining the cells in order to provide optical signal capable of quantitation by image analysis. Slamon uses two or more stained control cell pellets to relate the average optical signal from each pellet to the quantitative amount of target protein on the cells. Slamon discloses staining the cells using detectably-labeled antibodies directed against the target protein. The sample and control cell pellets are assayed at the same time so as to obtain a direct correlation between the amount of protein present in the cells per cell and the average optical density signal observed with the immunohistochemical staining. A calibration curve is prepared relating average optical signal observed with each pellet and the amount of target protein present in the pellet cells. The signal obtained from the

sample is related to the concentration curve relating signal to concentration, to concentration of the target protein with known amounts of the protein in the control cell pellets. Veltri is combined with Slamon only for the teaching of determining optical density of stained target protein per pixel of cell area, i.e. nuclear or cytoplasmic receptor cites, in a population of nucleated cells after immunostaining the target biomarker protein in the cells using biomarker specific antibody.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Veltri in determining optical density of stained target protein per pixel of cell area, into the method of Slamon because Veltri specifically taught that resulting values of such pixel measurement relate specifically to the target proteins specific in selected cell areas; thus, excludes measurement of nonspecific extraneous proteins.

C) Applicant argues that the Office has engaged in impermissible hindsight to support its argument.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon impermissible hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

D) Applicant argues that none of the cited references, either alone or in combination, teach the claimed invention and that the deficiencies of Slamon and Veltri are not overcome by the combination with McNamara. Applicant contends that McNamara discloses in situ analysis of a biological sample comprising the steps of staining the biological sample with three stains but does not provide a teaching related to determining average optical density of stained target protein per pixel of cellular area, nor generating a calibration curve relating the relating the known quantity of target protein with the average optical density of stained target protein per pixel of cellular area" or using such a calibration curve to determine the quantity of target protein in a biological sample. Applicant specifically contends that McNamara does not render claim 12 obvious when combined with the Slamon and Veltri references.

In as far as McNamara et al. failing to teach a method of determining an "average optical density of stained target protein per pixel of cellular area",

followed by either "generating a calibration curve relating the known quantity of target protein with the average optical density of stained target protein per pixel of cellular area" or using such a calibration curve to determine the quantity of target protein in a biological sample, which amounts to arguing against the reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

This rejection is based on the combination of Slamon and Veltri with McNamara. In this case, Slamon discloses a method of determining expression level of target protein in cells by immunohistochemically staining the cells in order to provide optical signal capable of quantitation by image analysis. Slamon uses two or more stained control cell pellets to relate the average optical signal from each pellet to the quantitative amount of target protein on the cells. The sample and control cell pellets are assayed at the same time so as to obtain a direct correlation between the amount of protein present in the cells per cell and the average optical density signal observed with the immunohistochemical staining. A calibration curve is prepared relating average optical signal observed with each pellet and the amount of target protein present in the pellet cells. The signal obtained from the sample is related to the concentration curve relating signal to concentration, to concentration of the target protein with known amounts of the protein in the control cell pellets. Veltri is combined with Slamon only for the teaching of determining optical density of stained target protein per pixel of cell

area, i.e. nuclear or cytoplasmic receptor cites, in a population of nucleated cells after immunostaining the target biomarker protein in the cells using biomarker specific antibody. McNamara is combined with Slamon and Veltri only for the disclosure of in situ analysis of biological samples using four different immunohistochemical stains and collecting spectral data wherein each spectrum is associated with a target protein, i.e. cytological marker, that is individually detectable. McNamara specifically discloses immunohistochemically staining control cells which are simultaneously co-stained with the biological sample, obtaining optical density measurements, and comparing results therebetween. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate multiple immunohistochemical staining as taught by McNamara into the cellular samples in the method of Slamon as modified by Veltri, wherein quantitative optical density measurement of target proteins is performed using image analysis because McNamara specifically taught that use of multiple immunohistochemical staining in combination with spectral imaging allows for simultaneous detection of a plurality of distinct components or target proteins present in a cell. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate multiple immunohistochemical staining as taught by McNamara into the cellular samples in the method of Slamon as modified by Veltri, wherein quantitative optical density measurement of target proteins is performed using image analysis because McNamara specifically taught that use of multiple immunohistochemical

staining in combination with spectral imaging allows for simultaneous detection of a plurality of distinct components or target proteins present in a cell.

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax

phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
September 6, 2004

Christopher L. Chin

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9/7/04